Optimizing the control of foot-and-mouth disease in Denmark by simulation

Meta-analysis on the efficacy of foot-and-mouth disease emergency vaccination

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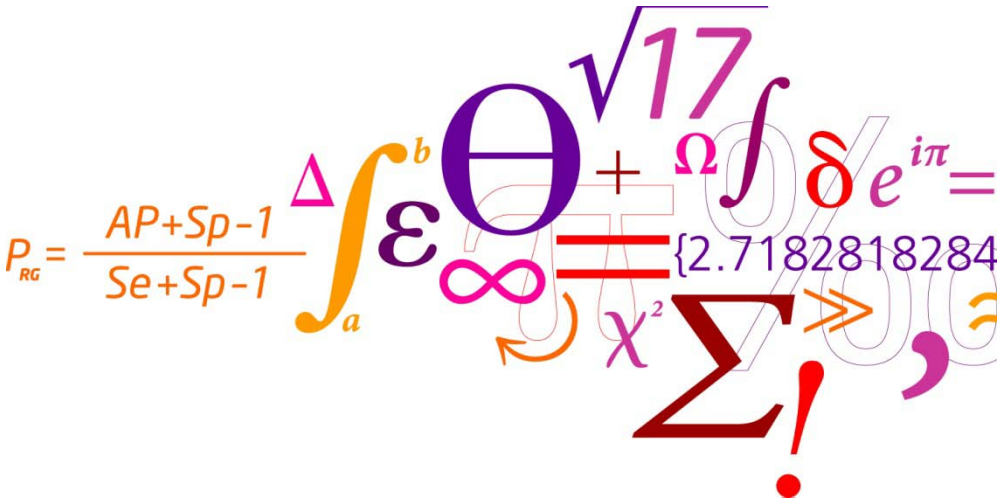

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Background

- EU member state must maintain the FMD free status. In case of an outbreak, animals within a defined area could be vaccinated.
- To estimate the epidemiologic and economic consequence of emergency vaccination, estimates of vaccine efficacy are important for simulation models.
- Several studies evaluated the efficacy of emergency vaccination. Variability between the estimates can be observed.

Objective

- Conduct a comprehensive assessment of the efficacy of emergency vaccination using meta-analysis of available literature.

What is meta-analysis?

- Statistical technique.
- Summarize the results of different studies that address a related hypothesis.
- Controls for study characteristics
- Results in an overall average are more powerful than outcomes of individual studies.

Characteristics of an emergency vaccine?

- Contain no residues of a live virus and have minimal side effects to newborns and adults
- After a single application with the recommended dose, achieve a potency dose 50 (PD50) of ≥ 6
- Be compatible with serological tests that identify infection in vaccinated animals
- Induce reasonably long lasting immunity and provide a broad spectrum of antigenic protection
- Be stable under storage once formulated
- Provide a rapid protection after vaccination
- Reduce the reproduction ratio (R0) to below 1

Inclusion criteria

- Experimental challenge with FMD emergency vaccination using cattle, swine, and/or sheep.
- Research or symposium papers published in English language.
- Report the number of protected animals and the total number of animals in
  - vaccinated group
  - non-vaccinated control group.
- Both groups should be challenged with a homologous virus.
- Several groups were contacted to obtain unpublished data.

Definition of efficacy

- Determine the efficacy of FMD emergency vaccination in terms of:
  - Clinical protection.
  - Virological protection.

Outcome parameters

- Parameters to represent protection:
  - Relative risk (**RR**) of clinical disease.
  - RR of infection.

RR of clinical disease

- RR = the incidence of clinical disease in the vaccinated group divided by the incidence in the non-vaccinated group.

- Incidence of clinical disease = number of clinically diseased animals divided by the total number of animals per group.

Infection

- Several tests were used to diagnose infection.
  - When an animal was positive to any of the tests, the animal was considered infected.
- The tests were:
  - Virus isolation from the blood, oral, nasal, or esophageal-pharyngeal fluid.
  - Presence of antibodies to non-structural proteins.
  - RT-PCR of oral, nasal, or esophageal-pharyngeal fluid.

RR of virological protection

- The RR of virological protection= the incidence of FMD infection in the vaccinated group divided by the incidence in the non-vaccinated group.
- The incidence = the number of FMD infected animals divided by the total number of animals per group.

Meta-analysis procedure

- A pooled RR was calculated for the clinical and virological protection for
  - Cattle
  - Swine
  - Sheep
- A random effect model was used to calculate the pooled RR.
  - This model corrects for the variability between studies due to known and unknown covariates.
- An analysis was conducted when at least 4 studies were available.

Publication bias

- Studies with large and interesting effects ⇒ more likely to be published
- Studies with small or no effects ⇒ not likely to be published

- Consequence: biased body of research.

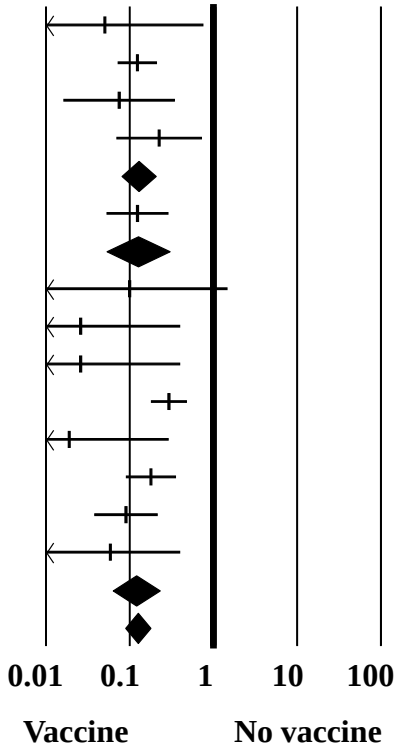
- Tests to detect publication bias:
  - a measures of study size relative to the study effect.

Results - descriptive

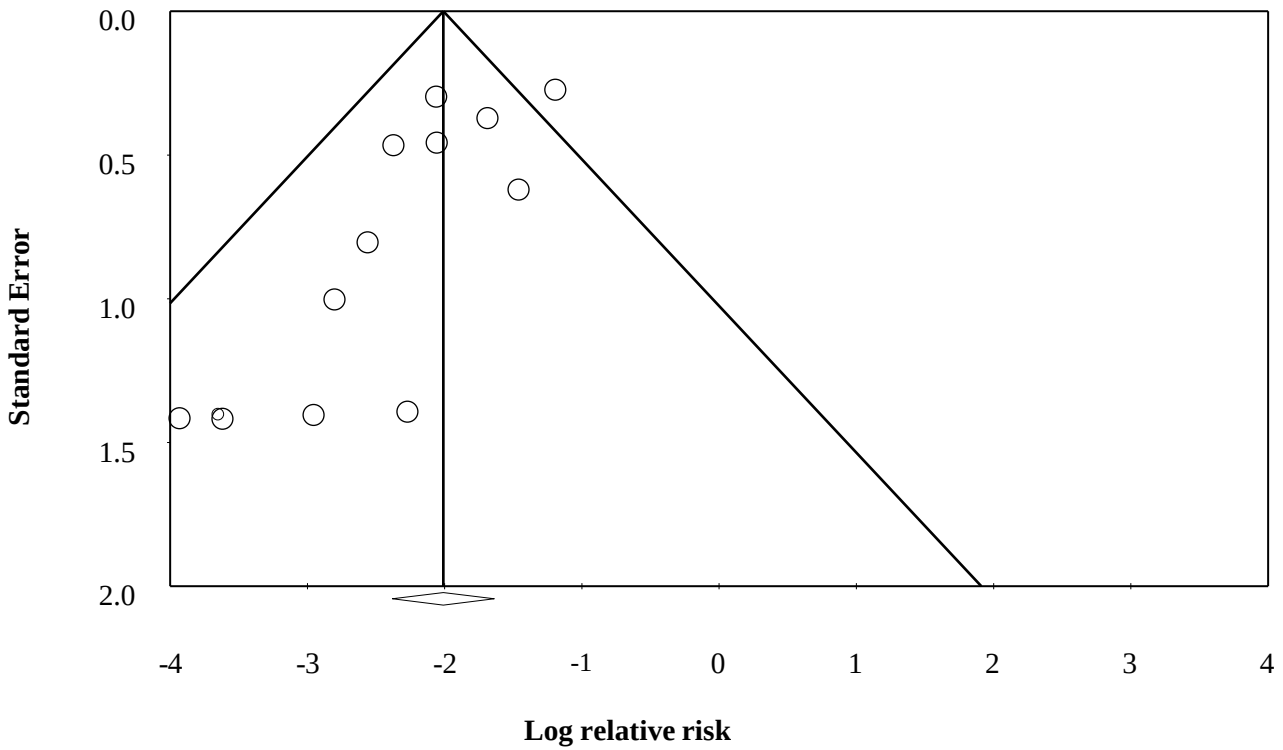
- 28 studies fitted the criteria.
- 27 studies included in the analyses.
- 10 conducted using cattle.
- 9 conducted using swine.
- 5 conducted using sheep.
- 3 had more than 1 species.
- 4 unpublished studies conducted on swine.

Results – Clinical protection in cattle

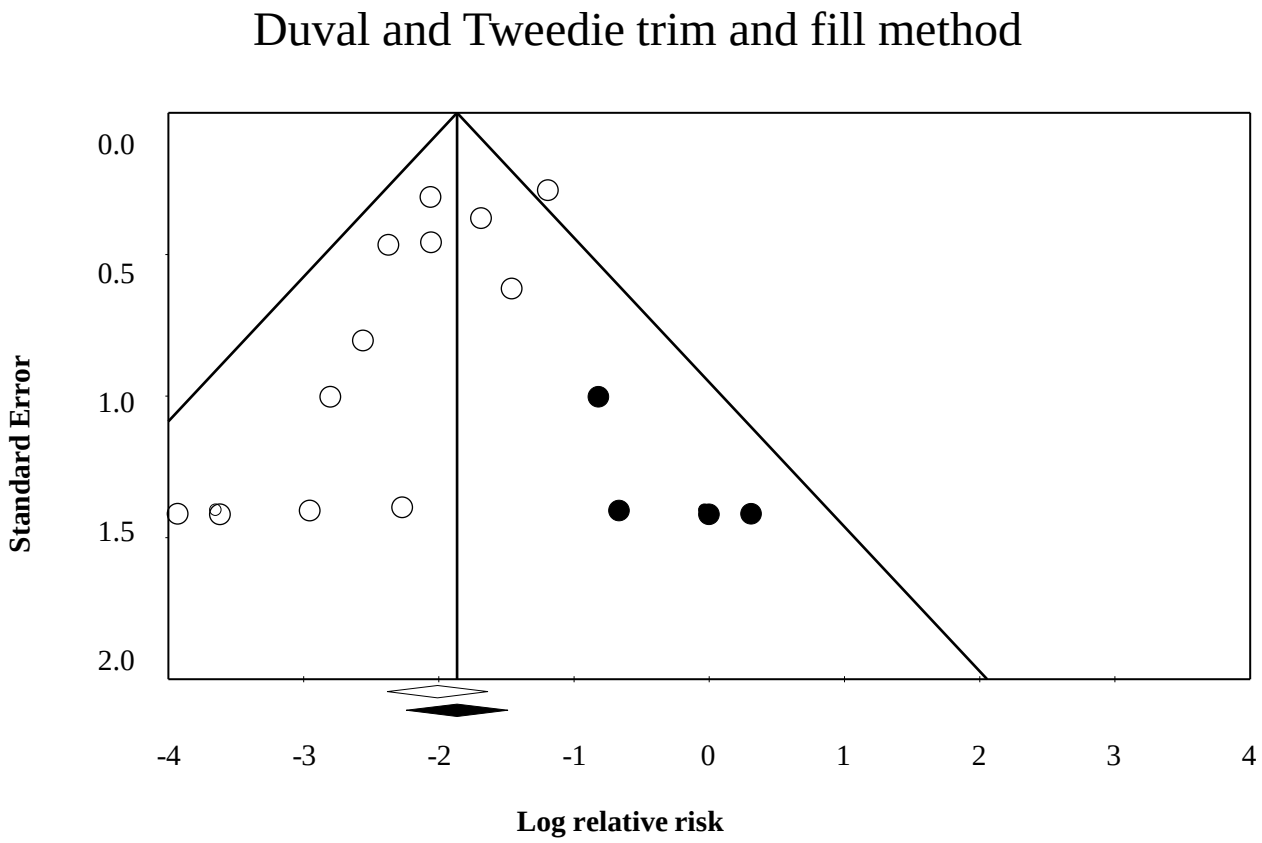
Virus serotype	Study	RR	Lower limit	Upper limit
A	Brehm, 2008	0.051	0.003	0.770
A	Goris, 2008	0.123	0.071	0.214
A	Graves, 1968	0.075	0.016	0.352
A	Mattion, 2004	0.225	0.069	0.737
Pooled RR A		**0.126**	**0.079**	**0.202**
Asia 1	Salt, 1995	0.124	0.052	0.295
Pooled RR Asia 1		**0.124**	**0.052**	**0.295**
O	Aggarwal, 2002	0.100	0.007	1.490
O	Cox, 2005	0.026	0.002	0.406
O	Cox, 2006	0.026	0.002	0.406
O	Cox, 2007	0.294	0.177	0.488
O	Doel, 1994	0.019	0.001	0.297
O	Donaldson, 1989	0.179	0.089	0.361
O	Goris, 2007	0.090	0.037	0.219
O	Orsel, 2005	0.059	0.008	0.408
Pooled RR O		**0.118**	**0.062**	**0.226**
Overall Pooled RR		**0.123**	**0.087**	**0.175**



Results – Clinical protection in cattle - publication bias



Results – Clinical protection in cattle - publication bias



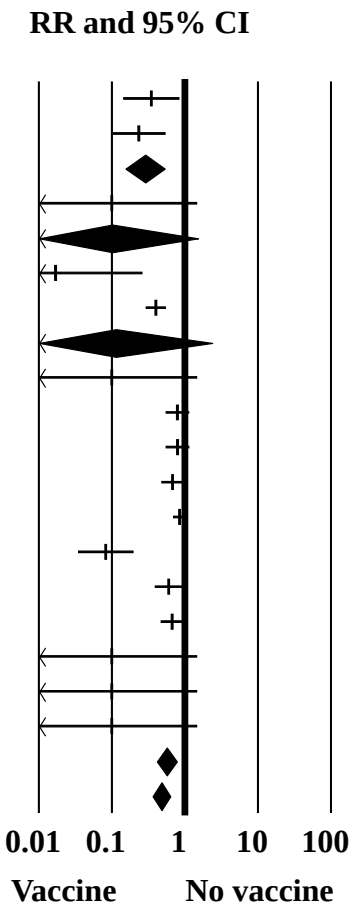
Results – Virological protection in cattle

- Vaccinated cattle
  - 0.65 (0.53 – 0.81) lower chance of FMD infection

- No significant publication bias was identified.

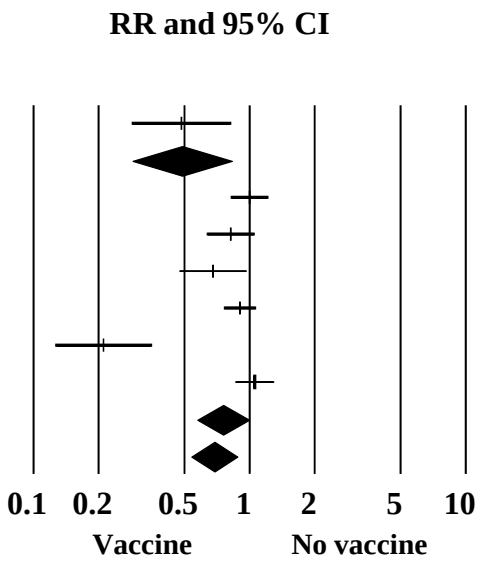
Results – Clinical protection in swine

Virus serotype	Study	RR	Lower limit	Upper limit
A	Buonavoglia, 1988	0.347	0.141	0.852
A	Graves, 1968	0.234	0.100	0.549
Pooled RR A		**0.282**	**0.152**	**0.524**
Asia	Unpublished 2	0.100	0.007	1.490
Pooled RR Asia		**0.100**	**0.007**	**1.490**
C	Salt, 1998	0.017	0.001	0.265
C	Sellers, 1976	0.400	0.288	0.556
Pooled RR C		**0.112**	**0.005**	**2.338**
O	Aggarwal, 2002	0.100	0.007	1.490
O	Barnett, 2002	0.789	0.537	1.160
O	Doel, 1994	0.792	0.538	1.164
O	Eble, 2004	0.677	0.470	0.976
O	Eble, 2007	0.845	0.683	1.045
O	Eble, 2009	0.083	0.034	0.200
O	Orsel, 2007	0.600	0.382	0.941
O	Parida, 2007	0.668	0.462	0.966
O	Unpublished 1	0.100	0.007	1.490
O	Unpublished 3	0.100	0.007	1.490
O	Unpublished 4	0.100	0.007	1.490
Pooled RR O		**0.559**	**0.408**	**0.767**
Overall Pooled RR		**0.472**	**0.357**	**0.623**



Results – Virological protection in swine

Virus serotype	Study	RR	Lower limit	Upper limit
C	Salt, 1998	0.484	0.285	0.821
PRR C		**0.484**	**0.285**	**0.821**
O	Barnett, 2002	1.000	0.818	1.223
O	Orsel, 2007	0.818	0.634	1.057
O	Eble, 2004	0.677	0.470	0.976
O	Eble, 2007	0.902	0.761	1.071
O	Eble, 2009	0.211	0.126	0.353
O	Parida, 2007	1.055	0.853	1.306
PRR O		**0.749**	**0.568**	**0.987**
Overall PRR		**0.682**	**0.534**	**0.871**



Results – Protection in sheep

- Vaccinated sheep had
  - 0.31 (0.18-0.53) lower chance to develop clinical disease and
  - 0.57 (0.39-0.82) lower chance of FMD infection
- No significant publication bias was identified in both analyses.

Conclusions

- Emergency vaccination provided clinical and virological protection against FMD in cattle, swine and sheep.
- No significant publication bias was identified in the analyses.
- The outcomes of the meta-analysis can be used for further economic assessment of emergency vaccination in case of an outbreak using simulation modeling.


THANK
YOU